

VU Research Portal

The Genetics of the Mood Disorder Spectrum

Coleman, Jonathan R I; Breen, Gerome; Bipolar Disorder Working Group of the Psychiatric Genomics Consortium; Abdellaoui, A.; Derks, E.M.; Dolan, C.V.; Hottenga, Jouke Jan ; Jansen, Rick; Mbarek, Hamdi; Middeldorp, C.M.; Milaneschi, Yuri; Nivard, Michel G.; Peyrot, Wouter J; Willemsen, Gonneke; Boomsma, D.I.; de Geus, Eco J.C.; W J H Penninx, Brenda; Posthuma, Danielle

published in
Biological Psychiatry
2020

DOI (link to publisher)
[10.1016/j.biopsych.2019.10.015](https://doi.org/10.1016/j.biopsych.2019.10.015)

document version
Publisher's PDF, also known as Version of record

document license
Article 25fa Dutch Copyright Act

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Coleman, J. R. I., Breen, G., Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Abdellaoui, A., Derks, E. M., Dolan, C. V., Hottenga, J. J., Jansen, R., Mbarek, H., Middeldorp, C. M., Milaneschi, Y., Nivard, M. G., Peyrot, W. J., Willemsen, G., Boomsma, D. I., de Geus, E. J. C., W J H Penninx, B., & Posthuma, D. (2020). The Genetics of the Mood Disorder Spectrum: Genome-wide Association Analyses of More Than 185,000 Cases and 439,000 Controls. *Biological Psychiatry*, 88(2), 169-184.
<https://doi.org/10.1016/j.biopsych.2019.10.015>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:
vuresearchportal.ub@vu.nl

Jonathan R.I. Coleman, H  l  na A. Gaspar, Julien Bryois, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, and Gerome Breen

BACKGROUND: Mood disorders (including major depressive disorder and bipolar disorder) affect 10% to 20% of the population. They range from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Multiple approaches have shown considerable sharing of risk factors across mood disorders despite their diagnostic distinction.

METHODS: To clarify the shared molecular genetic basis of major depressive disorder and bipolar disorder and to highlight disorder-specific associations, we meta-analyzed data from the latest Psychiatric Genomics Consortium genome-wide association studies of major depression (including data from 23andMe) and bipolar disorder, and an additional major depressive disorder cohort from UK Biobank (total: 185,285 cases, 439,741 controls; nonoverlapping $N = 609,424$).

RESULTS: Seventy-three loci reached genome-wide significance in the meta-analysis, including 15 that are novel for mood disorders. More loci from the Psychiatric Genomics Consortium analysis of major depression than from that for bipolar disorder reached genome-wide significance. Genetic correlations revealed that type 2 bipolar disorder correlates strongly with recurrent and single-episode major depressive disorder. Systems biology analyses highlight both similarities and differences between the mood disorders, particularly in the mouse brain cell types implicated by the expression patterns of associated genes. The mood disorders also differ in their genetic correlation with educational attainment—the relationship is positive in bipolar disorder but negative in major depressive disorder.

CONCLUSIONS: The mood disorders share several genetic associations, and genetic studies of major depressive disorder and bipolar disorder can be combined effectively to enable the discovery of variants not identified by studying either disorder alone. However, we demonstrate several differences between these disorders. Analyzing subtypes of major depressive disorder and bipolar disorder provides evidence for a genetic mood disorders spectrum.

Keywords: Affective disorders, Bipolar disorder, Genetic correlation, Genome-wide association study, Major depressive disorder, Mood disorders

Mood disorders affect 10% to 20% of the global population across their lifetime, ranging from brief episodes to incapacitating conditions that markedly impact lives (1–4). Major depressive disorder and bipolar disorder are the most common forms of mood disorder, and they have been grouped together since the publication of the DSM-III in 1980 (5). Although both disorders are given dedicated chapters in the DSM-5, they remain grouped as mood disorders in the ICD-11 (6,7).

Depressive episodes are common to major depressive disorder and type 2 bipolar disorder, and they are usually present in type 1 bipolar disorder (7). The bipolar disorders are distinguished from major depressive disorder by the presence of mania in type 1 bipolar disorder and hypomania in type 2 bipolar disorder (7). However, these distinctions are not absolute—some individuals with major depressive disorder develop bipolar disorder, and some endorse manic or

hypomanic symptoms (8–10). Following a first depressive episode, a nonremitting individual might develop bipolar disorder or recurrent major depressive disorder. Treatment guidelines for these disorders differ (11,12). Identifying shared and distinct genetic associations for major depressive disorder and bipolar disorder could aid our understanding of these diagnostic trajectories.

Twin studies suggest that 35% to 45% of variance in risk for major depressive disorder, and 65% to 70% for bipolar disorder, is accounted for by additive genetic factors (13). These genetic components are partially shared, with a twin genetic correlation (r_g) of approximately 65% and a common variant-based r_g of 30% to 35% derived from genome-wide association study (GWAS) results (14–17). Progress has been made in identifying specific genetic variants that underlie genetic risk. Recently, the Psychiatric Genomics Consortium (PGC) published the results

ISSN: 0006-3223

of a GWAS of bipolar disorder that included more than 20,000 cases, with 30 genomic loci reaching genome-wide significance (16). They also performed a GWAS of major depression that included more than 135,000 individuals with major depressive disorder and other definitions of depression, and found 44 loci reaching genome-wide significance (15). The PGC GWAS of major depression has since been combined with a broad depression GWAS (see [Supplemental Note](#) in [Supplement 1](#)).

GWASs have identified statistical associations of genetic loci with major depressive disorder and with bipolar disorder individually, but no GWAS has explored the genetic relationship between these disorders. In addition, both disorders exhibit considerable clinical heterogeneity and can be separated into subtypes. For example, the DSM-5 includes categories for type 1 and type 2 bipolar disorder, and for single-episode and recurrent major depressive disorder (7). We used the PGC analyses of major depression and bipolar disorder, along with analyses of formally defined major depressive disorder from the UK Biobank, to explore 2 aims (18,19). First, we sought to identify shared and distinct mood disorder genetics by combining studies of major depressive disorder and bipolar disorder. We then explored the genetic relationship of mood disorders to traits from the wider GWAS literature. Second, we assessed genetic similarities and differences between subtypes of bipolar disorder (from the PGC) and major depressive disorder (from the UK Biobank) through comparison of genetic correlations and polygenic risk scores.

METHODS AND MATERIALS

Participants

Our primary aim was to combine analyses of bipolar disorder and major depression to examine the shared and distinct genetics of these disorders. Full descriptions of each study and its composite cohorts are provided in previous articles (15,16,19). Brief descriptions are provided in [Supplement 1](#). Summary statistics were derived from participants of Western European ancestries, and unless otherwise specified are available at <https://www.med.unc.edu/pgc/results-and-downloads>.

Major depression data were drawn from the full cohort reported by Wray *et al.* (PGC MDD) (135,458 cases, 344,901 controls) (15). These included data from 23andMe (20), access to which requires a data transfer agreement; consequently, the data analyzed here differ from the publicly available summary statistics. Data for bipolar disorder were drawn from the discovery analysis previously reported (PGC BD) (20,352 cases, 31,358 controls), not including replication results (16).

Second, we wished to examine genetic correlations between mood disorder subtypes. Summary statistics were available for the primary bipolar disorder subtypes, type 1 bipolar disorder (BD1) (14,879 cases, 30,992 controls) and type 2 bipolar disorder (BD2) (3421 cases, 22,155 controls), and for schizoaffective bipolar disorder (SAB) (977 cases, 8690 controls), a mood disorder that includes psychotic symptoms. Controls were shared across these subtype analyses.

Subtype GWASs were not available from PGC MDD. Instead, a major depressive disorder cohort was derived from the online mental health questionnaire in the UK Biobank (UKB MDD) (29,475 cases, 63,482 controls) (resource 22 on <http://biobank.ctsu.ox.ac.uk>) (18). The definition of major depressive

disorder in this cohort is based on that in the DSM-5, as described in full elsewhere (18) and in [Table S1](#) in [Supplement 2](#) (7). Individuals meeting criteria for major depressive disorder were classified with recurrent major depressive disorder if they reported multiple depressed periods across their lifetime (rMDD) ($N = 17,451$ cases) and single-episode major depressive disorder otherwise (sMDD) ($N = 12,024$ cases) ([Table S1](#) in [Supplement 2](#)). Individuals reporting symptoms of depression but not meeting case criteria were excluded from the UKB MDD cohort but were used as a "subthreshold depression" subtype (subMDD) to examine the continuity of genetic associations with major depressive disorder below clinical thresholds ($N = 21,596$ cases). All subtypes were analyzed with all controls. Details on the quality control and analysis of the UK Biobank phenotypes are provided in [Supplement 1](#).

Meta-analysis of GWAS Data

We meta-analyzed PGC MDD and UKB MDD cohorts to obtain a single major depressive disorder GWAS (combined MDD cohort). We meta-analyzed the combined MDD cohort with PGC BD, comparing mood disorder cases with controls (MOOD). Further meta-analyses were performed between the PGC MDD cohort and each mood disorder subtype to assess the relative increase in variant discovery when adding different mood disorder definitions to the PGC MDD study ([Supplemental Methods](#) in [Supplement 1](#)).

Summary statistics were limited to common variants (minor allele frequency > 0.05) ([Supplemental Methods](#) in [Supplement 1](#)) genotyped or imputed with high confidence (INFO score > 0.6) in all studies. Controls were shared between PGC MDD and PGC BD studies, and (because the PGC MDD study included summary data) the extent of this overlap was unknown. Meta-analyses were therefore performed in METACARPA, which controls for sample overlap of unknown extent between studies using the variance-covariance matrix of the observed effect sizes at each variant, weighted by the sample sizes (21,22). METACARPA adjusted adequately for known overlap between cohorts ([Supplemental Methods](#) in [Supplement 1](#)). For later analyses (particularly linkage disequilibrium score regression [LDSC]), we used as the sample size a "nonoverlapping N " estimated for each meta-analysis ([Supplemental Methods](#) in [Supplement 1](#)). The definition, annotation, and visualization of each meta-analysis are described in [Supplemental Methods](#) in [Supplement 1](#).

Sensitivity Analysis Using Downsampled PGC MDD Data

Cross-trait meta-analyses may be biased if the power of the composite analyses differs substantially (23,24). The mean chi-square of the combined MDD cohort [1.7] exceeded that of PGC BD [1.39], suggesting that this bias may affect our results ([Table S2](#) in [Supplement 2](#)). We therefore repeated our analyses, meta-analyzing UKB MDD with summary statistics for PGC MDD that did not include participants from 23andMe nor the UK Biobank (mean chi-square = 1.35). All analyses were performed on the full and the downsampled analyses, with the exception of generalized summary-based Mendelian randomization (GSMR) analyses. Full results of the downsampled analyses are described in [Supplemental Results](#) in [Supplement 1](#).

Estimation of Single Nucleotide Polymorphism–Based Heritability and Genetic Correlations With Published GWASs

Single nucleotide polymorphism (SNP)–based heritability was assessed using LDSC (25). SNP-based heritability estimates were transformed to the liability scale, assuming population prevalences of 15% for the combined MDD cohort, 1% for the PGC BD cohort, and 16% for the MOOD cohort, and lower and upper bounds of these prevalences for comparison (Supplemental Methods in Supplement 1). LDSC separates genome-wide inflation into a component resulting from polygenicity and a component resulting from confounding (25). Inflation not due to polygenicity was quantified as $(\text{intercept} - 1)/(\text{mean observed } \chi^2 - 1)$ (26). Genetic correlations were calculated in LDSC between each analysis and 414 traits curated from published GWASs. Local estimates of SNP-based heritability and genetic covariance were obtained using the Heritability Estimator From Summary Statistics version 0.5.4b (Supplemental Methods and Supplemental Results in Supplement 1) (27,28).

Genetic Correlations Between Subtype Analyses

To assess the structure of genetic correlations within the mood disorders, SNP-based heritabilities and genetic correlations were calculated in LDSC between bipolar disorder subtypes (BD1, BD2, and SAB), and major depressive disorder subtypes (rMDD, sMDD, and subMDD). Putative differences between genetic correlations were identified using a z test ($p < .05$) and formally tested by applying a block jackknife with Bonferroni correction for significance ($p < .00083$) (Supplemental Methods in Supplement 1). Differences between the genetic correlations of the PGC MDD cohort and each bipolar disorder subtype, and between the PGC BD cohort and each major depressive disorder subtype, were also tested (Bonferroni correction for significance, $p < .0083$). Genetic correlations were hierarchically clustered using the *gplots* package in R, version 1.4.1 (29,30). Hierarchical clustering was performed using just the subtypes and including results from 6 external GWASs relevant to mood disorders (Supplemental Methods in Supplement 1) (31–35). To validate our conclusion of a genetic mood disorder spectrum, we performed principal component analysis of the genetic correlation matrix including the 6 external GWASs (Supplemental Methods and Results in Supplement 1).

Association of PGC BD Polygenic Risk Scores With MDD Subtypes

Polygenic risk score analyses were performed using PRSice2 to assess whether the rMDD cohort was genetically more similar to the PGC BD cohort than was the sMDD or subMDD cohort (Supplemental Methods in Supplement 1) (36).

Genewise, Gene-Set, and Tissue and Single-Cell Enrichment Analyses

For all analyses, the p values of SNPs in gene regions (defined as Ensembl gene locations) were combined as the aggregate of the mean and smallest p value to yield genewise p values, using MAGMA version 1.06 (Supplemental Methods and

Results in Supplement 1) (37). Gene-set analysis was performed in MAGMA (Supplemental Methods and Results in Supplement 1). Further analyses were performed to assess the enrichment of associated genes with expression-specificity profiles from tissues (Genotype-Tissue Expression project, version 7) and broadly defined (level 1) and narrowly defined (level 2) mouse brain cell types (38,39). Analyses were performed in MAGMA following previously described methods with minor modifications, with Bonferroni correction for significance (Supplemental Methods in Supplement 1) (38). Similar analyses can be performed in LDSC-SEG—we report MAGMA results, which reflect specificity of expression across the range, whereas LDSC-SEG compares the top 10% of the range with the remainder (40). Results using LDSC are included in Tables S9–S11 in Supplement 2.

Mendelian Randomization (GSMR)

Bidirectional Mendelian randomization analyses were performed using the GSMR option in GCTA to allow exploratory inference of the causal direction of known relationships between mood disorder traits and other traits (41,42). Specifically, we explored the relationships between the mood disorder analyses (MOOD, combined MDD, and PGC BD) and schizophrenia, intelligence, educational attainment, body mass index (BMI), and coronary artery disease (Supplemental Methods in Supplement 1) (32,43–46). These traits were previously examined in the PGC major depression GWAS—we additionally tested intelligence following the results of our genetic correlation analyses (15).

Conditional and Reversed-Effect Analyses

Additional analyses were performed to identify shared and distinct mood disorder loci, using mtCOJO, an extension of GSMR (Supplemental Methods in Supplement 1) (41,42). Analyses were performed on combined MDD conditional on PGC BD, and on PGC BD conditional on combined MDD (Supplemental Results in Supplement 1). To identify loci with opposite directions of effect between combined MDD and PGC BD, the MOOD meta-analysis was repeated with reversed direction of effects for PGC BD (Supplemental Methods and Results in Supplement 1).

RESULTS

Evidence for Confounding in Meta-analyses

Meta-analysis results were assessed for genome-wide inflation of test statistics using LDSC (25). Generally, the LDSC intercept was significantly >1 (1.00–1.06), which has previously been interpreted as confounding (Table S2 in Supplement 2). However, such inflation can occur in large cohorts without confounding (47). Estimates of inflation not due to polygenicity were small in all meta-analyses (4%–7%) (Table S2 in Supplement 2).

Combined MOOD Meta-analysis

We meta-analyzed the PGC MDD, PGC BD, and UKB MDD cohorts (MOOD cohort, cases = 185,285, controls = 439,741, nonoverlapping $N = 609,424$). In all, 73 loci reached genome-wide significance, of which 55 were also seen in the meta-

Table 1. Loci of Genome-wide Significance in the MOOD Meta-analysis^a

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	p Value	Previous Report
1	1	37192741	rs1002656	T	C	0.97	0.005	2.71×10^{-11}	DO, N
2	1	72837239	rs7531118	T	C	0.96	0.004	1.05×10^{-16}	D, DO, S, O
4	1	80795989	rs6667297	A	G	0.97	0.005	5.86×10^{-11}	D, DO
5	1	90796053	rs4261101	A	G	0.97	0.005	1.78×10^{-8}	D
6	1	175913828	rs10913112	T	C	0.97	0.005	1.46×10^{-10}	DO, O
7	1	177370033	rs16851203	T	C	0.96	0.007	2.38×10^{-9}	DO, S, O
9	2	22582968	rs61533748	T	C	0.97	0.004	3.84×10^{-11}	DO, N
10	2	57987593	rs11682175	T	C	0.97	0.004	2.18×10^{-11}	D, DO, BS, N, S, O
11	2	157111313	rs1226412	T	C	1.03	0.005	1.27×10^{-8}	D, DO, N, O
12	2	198807015	rs1518367	A	T	0.97	0.005	1.18×10^{-8}	BS, S, O
13	3	108148557	rs1531188	T	C	0.96	0.006	1.61×10^{-9}	O
14	3	158107180	rs7430565	A	G	0.97	0.004	2.30×10^{-11}	D, DO, N, O
16	4	42047778	rs34215985	C	G	0.97	0.006	1.72×10^{-10}	D, DO, N
17	5	77709430	rs4529173	T	C	0.97	0.005	4.29×10^{-9}	O
18	5	88002653	rs447801	T	C	1.03	0.004	2.29×10^{-10}	D, DO, N, O
19	5	92995013	rs71639293	A	G	1.03	0.005	5.85×10^{-9}	DO, N
20	5	103904226	rs12658032	A	G	1.04	0.005	2.19×10^{-16}	D, DO, N, O
21	5	106603482	rs55993664	A	C	0.97	0.006	1.87×10^{-8}	Novel locus
22	5	124251883	rs116755193	T	C	0.97	0.005	1.47×10^{-10}	D, O
23	5	164523472	rs11135349	A	C	0.97	0.004	2.96×10^{-11}	D, DO, N
24	5	166992078	rs4869056	A	G	0.97	0.005	5.21×10^{-9}	D
25	6	28673998	rs145410455	A	G	0.94	0.007	7.17×10^{-18}	D, DO, BO, BS, DS, N, S, O
26	6	101339400	rs7771570	T	C	0.97	0.004	9.68×10^{-10}	DO, N, O
27	6	105365891	rs1933802	C	G	0.98	0.004	1.05×10^{-8}	DO, S, O
28	7	12267221	rs4721057	A	G	0.97	0.004	7.31×10^{-11}	D, DO, N, O
29	7	24826589	rs79879286	C	G	1.04	0.006	1.97×10^{-11}	B, BS, DO, S
30	7	82514089	rs34866621	T	C	1.03	0.005	2.21×10^{-8}	DO, O
31	7	109099919	rs58104186	A	G	1.03	0.004	7.12×10^{-9}	D, DO
34	9	11379630	rs10959753	T	C	0.96	0.005	1.45×10^{-13}	D, DO, N, O
35	9	37207269	rs4526442	T	C	0.96	0.006	7.97×10^{-11}	DO, O
36	9	81413414	rs11137850	A	G	1.03	0.005	1.25×10^{-8}	Novel locus
38	9	119733380	rs10759881	A	C	1.03	0.005	8.56×10^{-9}	D, DO
40	9	122664468	rs10818400	T	G	0.98	0.004	1.29×10^{-8}	N
41	9	126682068	rs7029033	T	C	1.04	0.008	2.61×10^{-8}	D, DO, O
42	10	104684544	rs78821730	A	G	0.96	0.007	2.95×10^{-8}	N, BS, S, O
43	10	106563924	rs61867293	T	C	0.96	0.005	5.64×10^{-12}	D, DO, N, O
44	11	16293680	rs977509	T	C	0.97	0.005	1.19×10^{-8}	DO, N, O
45	11	31850105	rs1806153	T	G	1.03	0.005	2.81×10^{-9}	D, DO, N, O
46	11	32765866	rs143864773	T	C	1.04	0.008	1.70×10^{-8}	Novel locus
47	11	61557803	rs102275	T	C	0.97	0.005	5.04×10^{-11}	B, DO, BO, O
48	11	63632673	rs10792422	T	G	0.98	0.004	2.18×10^{-8}	O
49	11	88743208	rs4753209	A	T	0.97	0.004	4.15×10^{-9}	DO, N, O
50	11	99268617	rs1504721	A	C	0.98	0.004	2.24×10^{-8}	O
51	11	113392994	rs2514218	T	C	0.97	0.005	3.22×10^{-10}	DO, BS, N, S, O
52	12	2344644	rs769087	A	G	1.03	0.005	3.27×10^{-8}	B, BD, BO, DS, BS, S, O
53	12	23947737	rs4074723	A	C	0.97	0.004	3.18×10^{-9}	D, DO, N, O
54	12	121186246	rs58235352	A	G	0.95	0.009	1.64×10^{-10}	DO, O
55	12	121907336	rs7962128	A	G	1.02	0.004	3.63×10^{-8}	Novel locus
56	13	44327799	rs4143229	A	C	0.95	0.008	2.73×10^{-10}	D
57	13	53625781	rs12552	A	G	1.04	0.004	1.25×10^{-23}	D, DO, O
58	14	42074726	rs61990288	A	G	0.97	0.004	2.29×10^{-10}	D, DO, O
60	14	64686207	rs915057	A	G	0.98	0.004	1.92×10^{-8}	D, DO, O
61	14	75130235	rs1045430	T	G	0.97	0.004	9.83×10^{-11}	D, DO, N, O

Table 1. Continued

Locus	Chr	BP	Index SNP	A1	A2	OR	SE	p Value	Previous Report
62	14	104017953	rs10149470	A	G	0.97	0.004	1.15×10^{-10}	D, DS, DO, BS, S, O
63	15	36355868	rs1828385	A	C	0.97	0.004	1.15×10^{-8}	Novel locus
64	15	37643831	rs8037355	T	C	0.97	0.004	4.09×10^{-15}	D, DO, O
65	16	6310645	rs8063603	A	G	0.97	0.005	5.36×10^{-11}	D, DO
66	16	7667332	rs11077206	C	G	1.03	0.004	5.49×10^{-10}	D, DO, N, O
67	16	13038723	rs12935276	T	G	0.97	0.005	4.75×10^{-10}	D, DO, N, O
68	16	13750257	rs7403810	T	G	1.03	0.005	7.52×10^{-11}	DO, BS, S, O
69	16	72214276	rs11643192	A	C	1.03	0.004	1.46×10^{-11}	D, O
70	17	27363750	rs75581564	A	G	1.04	0.006	2.47×10^{-10}	D, DO, O
71	18	31349072	rs4534926	C	G	1.03	0.004	9.14×10^{-9}	DO, N
72	18	36883737	rs62099069	A	T	0.97	0.004	9.52×10^{-10}	D, O
73	18	42260348	rs117763335	T	C	0.97	0.005	1.33×10^{-8}	O
74	18	50614732	rs11663393	A	G	1.03	0.004	1.56×10^{-10}	D, DO, N, O
75	18	52517906	rs1833288	A	G	1.03	0.005	4.54×10^{-8}	D, DS, DO, N, S, O
76	18	53101598	rs12958048	A	G	1.04	0.005	4.86×10^{-14}	D, DO, BS, N, S, O
77	19	30939989	rs33431	T	C	1.02	0.004	4.04×10^{-8}	DO, O
78	20	45841052	rs910187	A	G	0.97	0.005	3.09×10^{-9}	DO, O
79	22	41621714	rs2179744	A	G	1.03	0.005	3.83×10^{-12}	D, B, DO, BS, N, S, O
80	22	42815358	rs7288411	A	G	1.03	0.005	3.86×10^{-8}	Novel locus
81	22	50679436	rs113872034	A	G	0.96	0.006	1.10×10^{-9}	O

A1, effect allele; A2, noneffect allele; B, locus previously implicated in Psychiatric Genomics Consortium bipolar disorder study; BD, locus previously implicated in previous combined studies of bipolar disorder and major depressive disorder; BO, locus previously implicated in other studies of bipolar disorder; BP, base position; BS, locus implicated in previous combined studies of bipolar disorder and schizophrenia; Chr, chromosome; D, locus previously implicated in Psychiatric Genomics Consortium major depressive disorder study; DO, locus previously implicated in other studies of major depressive disorder or depressive symptoms; DS, locus implicated in previous combined studies of major depressive disorder and schizophrenia; Locus, shared locus number for annotation (Table S3 in Supplement 2); MOOD, combined major depressive disorder cohorts with Psychiatric Genomics Consortium bipolar disorder cohort; N, locus previously implicated in studies of neuroticism; O, locus previously implicated in other studies (see Table S4 in Supplement 2); OR, odds ratio; S, locus previously implicated in studies of schizophrenia; SE, standard error; SNP, single nucleotide polymorphism.

^aGenome-wide significance $p < 5 \times 10^{-8}$.

analysis of PGC MDD and UKB MDD (combined MDD cohort) (Table 1, Table S3 in Supplement 2, and Figures S1–S8 in Supplement 1). Of the 44 PGC MDD loci, 39 reached genome-wide significance in the MOOD analysis. In comparison, only 4 of the 19 PGC BD loci reached genome-wide significance in the MOOD analysis (Table S3 in Supplement 2). MOOD loci overlapped considerably with those found in previous studies of depression and depressive symptoms (51 of 73 loci) (20,23,48–52), bipolar disorder (3 of 73 loci) (53–56), neuroticism (32 of 73 loci) (23,57–59), and schizophrenia (15 of 73 loci) (32,60), although there is overlap between the participants in the MOOD cohort and participants in many of these studies. Locus 52 (chromosome 12) passed genome-wide significance in a previous meta-analysis of broad depression and bipolar disorder, although the 2 other loci from this study did not replicate (51). Of the 73 associations, 6 loci are entirely novel ($p > 5 \times 10^{-8}$ in previous studies of all phenotypes) (Table 1; Table S4 in Supplement 2).

Downsampled MOOD data (cases = 95,481, controls = 287,932, nonoverlapping $N = 280,214$) showed increased similarity to PGC BD data compared with MOOD data but remained more similar to PGC MDD data. Nineteen loci reached genome-wide significance in the analysis of downsampled MOOD data, including 9 (20%) from the PGC MDD analysis, compared with 2 (11%) reported in the PGC BD

findings (Table S3 in Supplement 2). Of 19 loci, 17 were also observed in the MOOD analysis. Of the 2 loci not observed in the MOOD study, 1 passed genome-wide significance in the PGC BD study.

SNP-Based Heritability and Genetic Correlations

The estimate of SNP-based heritability for the MOOD cohort (8.8%) was closer to that for the PGC MDD cohort (8.8%) than for the PGC BD cohort (20%). Significant genetic correlations between the MOOD cohort and other traits included psychiatric and behavioral, reproductive, cardiometabolic, and sociodemographic traits (Figure 1 and Table S5 in Supplement 2). Genetic correlations with psychiatric and behavioral traits are consistently observed across psychiatric traits (17,61). The genetic correlation between the MOOD cohort and educational attainment was -0.06 ($p = .004$), intermediate between the results of the combined MDD analysis ($r_g = -.11$) and those of the PGC BD analysis ($r_g = .19$) (Table S6 in Supplement 2). Notably, the genetic correlation with intelligence was not significant in any of the 3 analyses ($p > 1.27 \times 10^{-4}$). However, sensitivity analyses (see below) indicated that including 23andMe data in the PGC MDD analysis obscured a negative genetic correlation with intelligence.

A

	Mood disorders	Down-sampled mood disorders	PGC + UK Biobank Major depressive disorder	Down-sampled Major depressive disorder	Bipolar disorder
PGC (2018) Major depressive disorder	1	0.95	1	1	0.34
PGC (2019) Bipolar disorder	0.55	0.75	0.35	0.38	1
PGC (2014) Schizophrenia European-only	0.48	0.61	0.35	0.4	0.7
PGC (2013) Cross-disorder analysis	0.69	0.86	0.54	0.61	0.82
UK Biobank Lifetime anxieties	0.76	0.66	0.77	0.72	0.31
PGC-iPSYCH (2017) Attention-deficit hyperactivity disorder	0.43	0.48	0.45	0.54	0.14
Wellbeing spectrum	-0.85	-0.8	-0.87	-0.89	-0.28

B

	Mood disorders	Down-sampled mood disorders	PGC + UK Biobank Major depressive disorder	Down-sampled Major depressive disorder	Bipolar disorder
Insomnia	0.41	0.39	0.44	0.48	0.05
Years of schooling (2018)	-0.06	-0.07	-0.11	-0.2	0.19
Intelligence (2017)	-0.05	-0.13	-0.05	-0.15	-0.04
Coronary artery disease	0.14	0.16	0.15	0.22	0.02
Age at first birth	-0.27	-0.27	-0.3	-0.36	0
GIANT + UK Biobank (2018) Body mass index	0.1	0.06	0.13	0.13	-0.06
UK Biobank Household income	-0.26	-0.3	-0.3	-0.43	-0.05

Figure 1. Selected genetic correlations of **(A)** psychiatric traits and **(B)** other traits with the main meta-analysis (MOOD cohort), the separate mood disorder analyses (combined major depressive disorder cohorts and Psychiatric Genomics Consortium [PGC] bipolar disorder cohort), and the downsampled analyses (down-sampled MOOD cohort, downsampled major depressive disorder cohort). Full genetic correlation results are provided in [Table S5](#) in [Supplement 2](#). GIANT, The Genetic Investigation of Anthropometric Traits consortium; iPSYCH, Lundbeck Foundation Initiative for Integrative Psychiatric Research.

The SNP-based heritability of downsampled MOOD data from LDSC was 11%, closer to PGC MDD results than to PGC BD results (Table S2 in Supplement 2). Genetic correlations varied (Tables S5 and S7 in Supplement 2), with some more similar to those of the PGC BD cohort (schizophrenia: downsampled $r_g = .61$, combined MDD $r_g = .35$, PGC BD $r_g = .7$) and others more similar to those of the combined MDD cohort (attention-deficit/hyperactivity disorder: downsampled $r_g = .48$, combined MDD $r_g = .45$, PGC BD $r_g = .14$). The genetic correlation with intelligence was significant ($r_g = -.13$, $p = 5 \times 10^{-7}$), because the excluded 23andMe depression cohort has a positive genetic correlation with intelligence ($r_g = .06$, $p = .01$). The greater genetic correlation of the MOOD cohort with the combined MDD cohort ($r_g = .98$) compared with the PGC BD cohort ($r_g = .55$) persisted when we compared the downsampled MOOD cohort with the combined MDD cohort ($r_g = .85$) and the PGC BD cohort ($r_g = .75$) (Table S6 in Supplement 2).

Relationship Between Mood Disorder Subtypes

Analyses were performed using GWAS data from subtypes of bipolar disorder (BD1, BD2, and SAB) and major depressive disorder (rMDD, sMDD, and subMDD). SNP-based heritability for the subtypes were 8% for subMDD and sMDD, 10% for BD2, 12% for rMDD, 22% for BD1, and 29% for SAB (Figure 2 and Table S2 in Supplement 2).

The major depressive disorder subtypes were strongly and significantly genetically correlated ($r_g = .9-.94$, $p_{rg} = 0 < .00083$). These correlations did not differ significantly from 1 (all $p_{rg} = 1 > .3$), nor from each other (all $p_{\Delta rg} = 0 > .5$) (Figure 2 and Table S8 in Supplement 2). BD1 and SAB were strongly correlated ($r_g = .77$, $p_{rg} = 0 = 6 \times 10^{-13}$, $p_{rg} = 1 = .03$), as were BD1 and BD2 ($r_g = .86$, $p_{rg} = 0 = 3 \times 10^{-16}$, $p_{rg} = 1 = .2$). However, BD2 was not significantly correlated with SAB ($r_g = .22$, $p_{rg} = 0 = .02$).

In hierarchical clustering, BD2 clustered with the major depressive disorder subtypes rather than the bipolar disorder subtypes. The strength of correlation between BD2 and BD1 did not differ from that between BD2 and rMDD ($r_g = .68$, $p_{rg} = 0 = 3 \times 10^{-8}$, $p_{rg} = 1 = .01$), following multiple testing correction ($\Delta r_g = .18$, $p = .02$). Overall, these results suggest that a spectrum of genetic relationships exist between major depressive disorder and bipolar disorder, with type 2 bipolar disorder bridging the two disorders (Figure 3 and Figure S9 in Supplement 1). This spectrum remained when 6 external phenotypes were added, and it was supported by results from principal component analysis (Supplemental Results and Figure S10 in Supplement 1).

Polygenic risk score analyses showed that individuals with high polygenic risk scores for bipolar disorder were more likely to report recurrent major depressive disorder than single-episode major depressive disorder, and more likely to report single-episode major depressive disorder than subthreshold depression (Supplemental Results in Supplement 1).

Tissue and Cell-Type Specificity Analyses

The results of genewise and gene-set analyses are described in Supplemental Results in Supplement 1. The tissue specificity of associated genes differed minimally between the analyses (Table S9 in Supplement 2). All brain regions were significantly enriched in all analyses, and the pituitary was also enriched in the combined MDD and PGC BD cohorts ($p < .000943$, Bonferroni correction for 53 regions) (Table S9 in Supplement 2). Results from downsampled MOOD and downsampled MDD analyses were generally consistent with those of the main analyses, except spinal cord was not enriched in either, nor was the cordate enriched in the downsampled MDD analysis.

In contrast, cell type enrichments differed between the combined MDD and PGC BD cohorts (Figure 4 and Tables S10

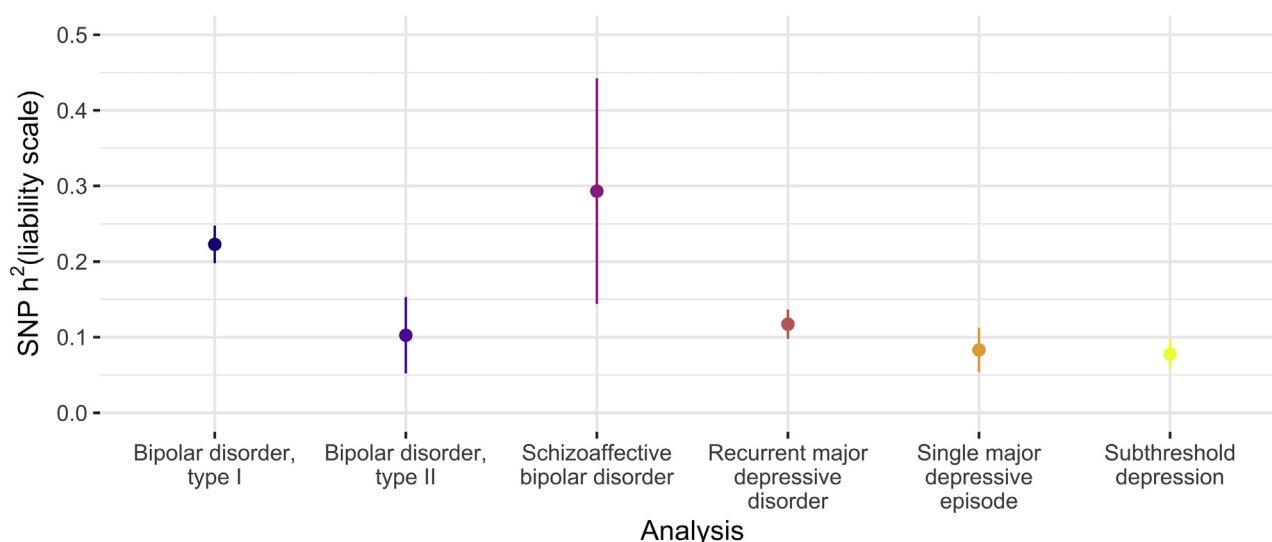


Figure 2. Single nucleotide polymorphism (SNP)-based heritability estimates for the subtypes of bipolar disorder and subtypes of major depressive disorder. Points represent SNP-based heritability estimates. Lines represent 95% confidence intervals. Full SNP-based heritability results are provided in Table S2 in Supplement 2.

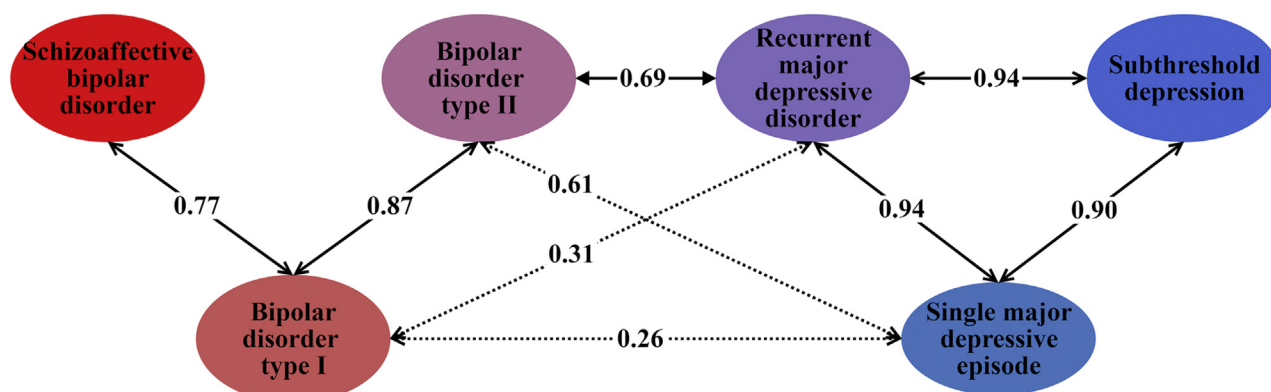


Figure 3. Genetic correlations across the mood disorder spectrum. Labeled arrows show genetic correlations that are significantly different from 0. Solid arrows represent genetic correlations that are not significantly different from 1 ($p < .00333$, Bonferroni correction for 15 tests). Full results are provided in Table S8 in Supplement 2.

and S11 in Supplement 2). Genes associated in the PGC BD cohort were enriched for expression in pyramidal cells from the CA1 region of the hippocampus and the somatosensory cortex and in striatal interneurons. None of these enrichments was significant in the combined MDD analysis. Genes associated only in the combined MDD cohort were significantly enriched for expression in neuroblasts and dopaminergic neurons from adult mice. Additional cell types (dopaminergic neuroblasts; dopaminergic, gamma-aminobutyric acidergic, and midbrain nucleus neurons from embryonic mice; interneurons; and medium spiny neurons) were enriched in both combined MDD and PGC BD cohorts, but the rank and strength of enrichment differed, most notably for medium spiny neurons. The general pattern of differences persisted when comparing the PGC BD analysis with the downsampled MDD analysis, although genes associated in the downsampled MDD cohort were not enriched for expression in adult dopaminergic neurons, embryonic midbrain nucleus neurons, interneurons, or medium spiny neurons (Figure S11 in Supplement 1).

Shared and Distinct Relationships With Mood Disorders and Inferred Causality

Bidirectional Mendelian randomization was used to investigate previously described relationships between mood disorder phenotypes (combined MDD cohort and PGC BD cohort) and external traits: schizophrenia, educational attainment, intelligence, BMI, and CAD (Figure 5 and Table S12 in Supplement 2). Associations with the PGC BD cohort should be interpreted cautiously, as only 19 loci reached genome-wide significance, several of which were removed as potentially pleiotropic in the analyses below.

Positive bidirectional relationships were observed between combined MDD, PGC BD, and schizophrenia. This finding is consistent with psychiatric disorders causing further psychiatric disorders or being correlated with other causal risk factors, including (but not limited to) a shared genetic basis.

Educational years were found to have a negative bidirectional relationship with combined MDD but a positive bidirectional relationship with PGC BD (albeit with only nominal

significance from PGC BD to educational years). In contrast, no significant relationship was observed between mood phenotypes and intelligence. This finding is consistent with differing causal roles of education (or its correlates) on the mood disorders, with a weaker reciprocal effect of the mood disorders altering the length of education.

A positive association was seen between BMI and the combined MDD cohort but not from the combined MDD cohort to BMI. In contrast, only a nominally significant negative relationship was seen from the PGC BD cohort to BMI. A positive association was observed from the combined MDD cohort to CAD; no relationship was observed between CAD and the PGC BD cohort.

DISCUSSION

We identified 73 genetic loci by meta-analyzing cohorts of major depressive disorder and bipolar disorder, including 15 loci novel to mood disorders. Our mood disorders meta-analysis results (MOOD cohort) are more like our major depressive disorder analysis (combined MDD cohort) than like our bipolar disorder analysis (PGC BD cohort). Partly, this finding results from the greater power of the major depressive disorder analysis compared with that of the bipolar disorder analysis. Nevertheless, genetic associations from our sensitivity analysis with equivalently powered cohorts (using downsampled MDD instead of combined MDD data) still showed a greater similarity to associations from major depressive disorder rather than bipolar disorder.

This finding may reflect a complex genetic architecture in bipolar disorder, wherein one set of variants may be associated more with manic symptoms and another set with depressive symptoms. Variants associated more with mania may have higher effect sizes, detectable at current bipolar disorder GWAS sample sizes, and may not be strongly associated with major depressive disorder. These differences could contribute to the higher heritability of bipolar disorder compared with major depressive disorder and would be consistent with reports that most of the genetic variance for mania is not shared with depression (13,14). Meta-analysis of

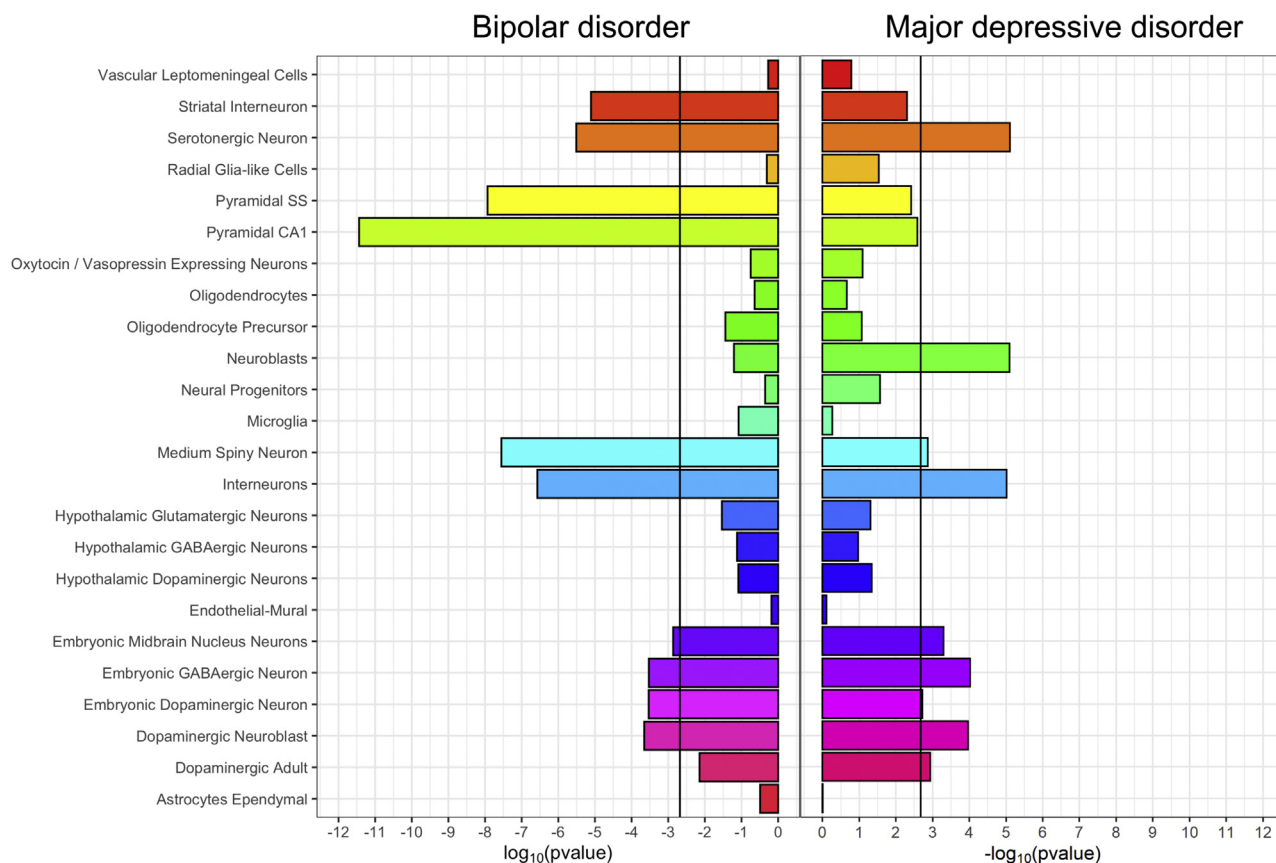


Figure 4. Cell-type expression specificity of genes associated with bipolar disorder (Psychiatric Genomics Consortium bipolar disorder study, left panel) and major depressive disorder (combined major depressive disorder studies, right panel). Black vertical lines represent significant enrichment ($p < .002$, Bonferroni correction for 24 cell types). See Table S10 in Supplement 2 for full results. GABAergic, gamma-aminobutyric acidergic; SS, somatosensory cortex.

bipolar disorder and major depressive disorder cohorts would support variants associated more with depression but not those associated with mania. This is consistent with our findings, and with depressive symptoms being both the unifying feature of the mood disorders and the core feature of major depressive disorder.

We examined the genetic relationship between mood disorder subtypes, including adding relevant external traits for context (Supplemental Results in Supplement 1). Type 2 bipolar disorder showed greater genetic similarity to major depressive disorder compared with type 1 bipolar disorder, mirroring similar findings from polygenic risk scores analyses (16,56). Individuals with high polygenic risk scores for bipolar disorder were more likely to report recurrent major depressive disorder than single-episode major depressive disorder. However, the genetic correlation of bipolar disorder with recurrent major depressive disorder was not significantly greater than that with single-episode major depressive disorder. This finding might reflect the difference in power between these methods. Genetic correlations between mood disorder subtypes support a genetic mood spectrum, with the schizophrenia-like type 1 bipolar disorder and schizoaffective bipolar disorder at one pole and the depressive disorders at the other, with type 2 bipolar disorder occupying an intermediate position.

Conditional and reversed-effect analyses (Supplemental Results in Supplement 1) suggest that few of the loci we identified are disorder specific. Nonetheless, we observed some genetic differences between the mood disorders. The expression specificity of associated genes in mouse brain cell types differed between bipolar disorder and major depressive disorder. Cell types more associated with bipolar disorder (pyramidal neurons and striatal interneurons) were also enriched in analyses of schizophrenia (38). Cell types more associated in major depressive disorder (neuroblasts, adult dopaminergic neurons, embryonic gamma-aminobutyric acidergic neurons) had weaker enrichments in schizophrenia but were enriched in analyses of neuroticism (57). The higher rank of serotonergic neurons in major depressive disorder compared with that in bipolar disorder is striking given the use of drugs targeting the serotonergic system in treating depression (62). Nevertheless, cell-type enrichment analyses require cautious interpretation, especially given the use of nonhuman reference data (38,63).

We explored potential causal relationships between the mood disorders and other traits using Mendelian randomization. Interpreting these analyses is challenging, especially for complex traits, when the ascertainment of cases varies, and when few (<20) variants are used as instruments (as in the PGC BD and downsampled analyses presented) (41,64,65). Mood disorders demonstrate considerable heterogeneity,

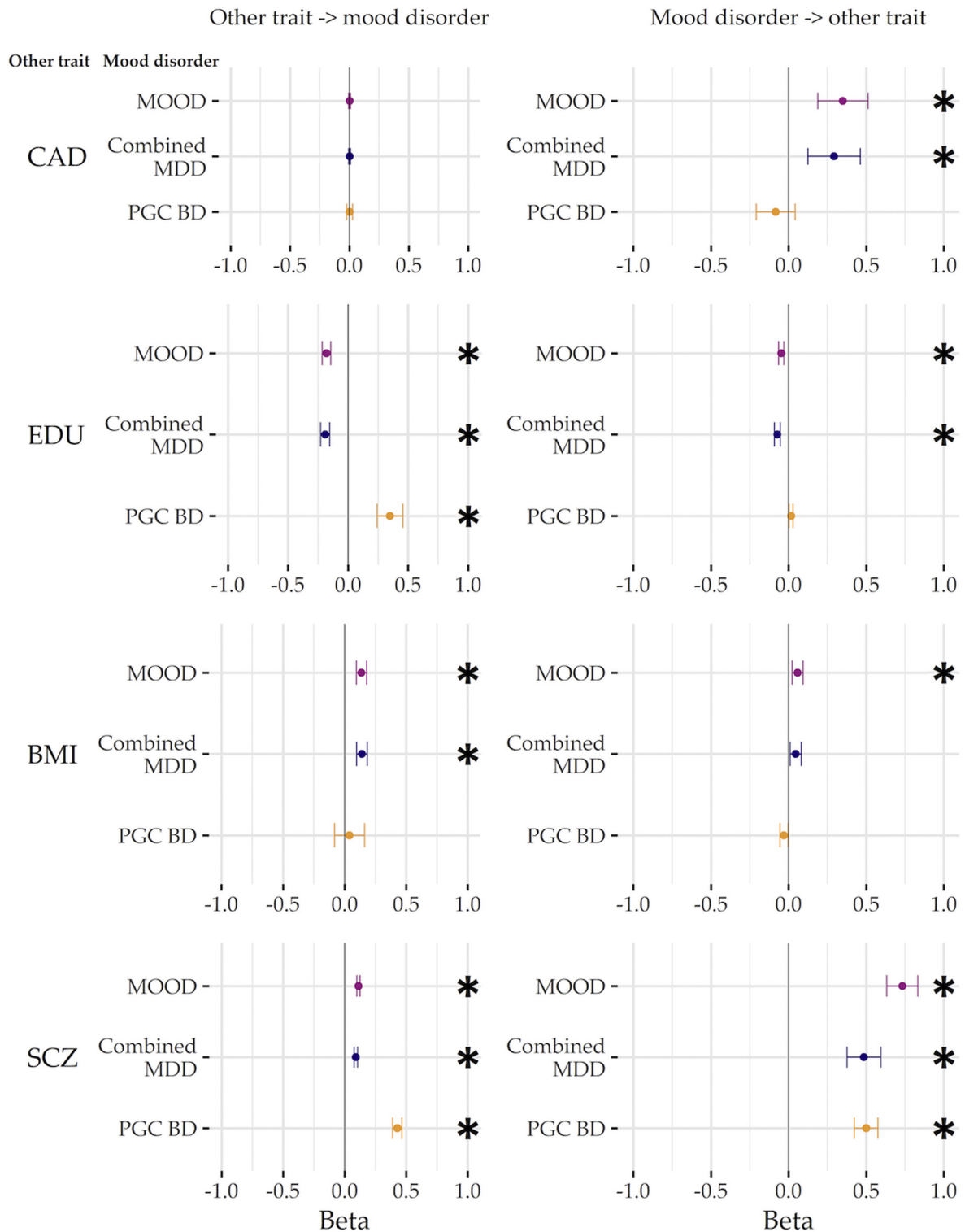


Figure 5. Generalized summary-based Mendelian randomization results from analyses with the main meta-analysis (MOOD), and the major depressive disorder and bipolar disorder analyses (combined major depressive disorder [combined MDD] cohort and Psychiatric Genomics Consortium bipolar disorder [PGC BD] cohort). External traits are coronary artery disease (CAD), educational attainment (EDU), body mass index (BMI), and schizophrenia (SCZ). β values are on the scale of the outcome genome-wide association study (logit for binary traits, phenotype scale for continuous). * $p < .004$ (Bonferroni correction for 2-way comparisons with 6 external traits). For figure data, including the number of nonpleiotropic single nucleotide polymorphisms included in each instrument, see Table S12 in Supplement 2.

potentially confounding the results of Mendelian randomization. That said, our results are consistent with a bidirectional influence of educational attainment on risk for mood disorders (and vice versa), with different directions of effect in major depressive disorder and bipolar disorder. We found no significant relationship between intelligence and either mood disorder. We also find results consistent with major depressive disorder increasing the risk for coronary artery disease in a relatively well-powered analysis. This mirrors epidemiological findings, although the mechanism remains unclear (66).

Despite the presence of depressive episodes, the mood disorders are diagnostically distinct, with differing epidemiology—for example, more women than men experience major depressive disorder, whereas diagnoses of bipolar disorder are roughly equal between the sexes (3). Differences in our genetic results between major depressive disorder and bipolar disorder may result from epidemiological heterogeneity rather than distinct biological mechanisms (67). Deeper phenotyping of GWAS datasets is ongoing, and such work will enable the effect of such confounding factors to be estimated in future studies (68).

We extend previous findings showing genetic continuity across the mood disorders (15–17,56). Combined mood disorder analyses may increase variant discovery, as well as the discovery of shared and distinct neurobiological gene sets and cell types. Our results indicate some genetic differences between major depressive disorder and bipolar disorder, including opposite bidirectional relationships of each with educational attainment, a possible influence of major depressive disorder on coronary artery disease risk, and differing mouse brain cell types implicated by the enrichment patterns of associated genes in each disorder. Finally, our data are consistent with a genetic mood disorder spectrum with separate clusters for type 1 bipolar disorder and for depressive disorders, linked by type 2 bipolar disorder, and with depression as the common symptom. The identification of specific sets of genetic variants differentially associated with depression and with mania remains an aim for future research.

ACKNOWLEDGMENTS AND DISCLOSURES

This study represents independent research partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley National Health Service (NHS) Foundation Trust and King's College London. High-performance computing facilities were funded with capital equipment grants from the Guy's and St. Thomas' Charity (Grant No. TR130505) and Maudsley Charity (Grant No. 980). The PGC has received major funding from the United States National Institute of Mental Health (NIMH) and the United States National Institute of Drug Abuse of the National Institutes of Health (NIH) (Grant Nos. U01 MH109528 [to PFS], U01MH109514 [to MCO], and U01 MH1095320 [to A Agrawal]). We acknowledge the continued support of the NL Genetic Cluster Computer (<http://www.geneticcluster.org/>) hosted by SURFsara in the management and curation of PGC data, with funding from Scientific Organization Netherlands (Grant No. 480-05-003 [to DP]). Central analysis of PGC data was funded by UK Medical Research Council (MRC) Centre and Program Grants (Grant Nos. G0801418 and G0800509 [to PAH, MCO, MJO]) and grants from the Australian National Health and Medical Research Council (NHMRC) (Grant Nos. 1078901 and 108788 [to NRW]). GB, JRIC, HAG, and CL were supported in part by the NIHR as part of the Maudsley BRC. DP is funded by the Dutch Brain Foundation and the VU University Amsterdam Netherlands. PFS receives support from the Swedish Research Council (Vetenskapsrådet) (Grant No. D0886501).

Acknowledgments and funding for individual cohorts follow (full expansions of individual cohort names can be found in the original PGC publications) (15,16). BD_TRS: This work was funded by the Deutsche Forschungsgemeinschaft (Grant Nos. FOR2107 DA1151/5-1, SFB-TRR58, and Project C09 [to UD]) and the Interdisciplinary Center for Clinical Research of the medical faculty of Münster (Grant No. Dan3/012/17 [to UD]). BiGS: Research was funded by the NIMH for work at 4 locations: Chicago (Grant No. R01 MH103368 [to ESG]), NIMH (Grant Nos. R01 MH061613 and ZIA MH002843 [to FJM]), Pittsburgh (Grant No. MH63480 [to VN]), and University of California–San Diego (Grant Nos. MH078151, MH081804, and MH59567 [to JK]). FJM was supported by the NIMH Intramural Research Program, NIH, and Department of Health and Human Services. BOMA-Australia: Funding was supplied by the Australian NHMRC (Grant Nos. 1037196, 1066177, and 1063960 [to JMF], Grant No. 1103623 [to SEM], Grant No. 1037196 [to PBM], Grant No. 1078399 [to GWM], Grant No. 1037196 [to PRS]). BOMA-Germany I, BOMA-Germany II, BOMA-Germany III, PsyCourse, and Münster MDD Cohort: This work was supported by the German Ministry for Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med program (Grant No. 01ZX1314A/01ZX1614A [to MMN and SC], Grant No. 01ZX1314G/01ZX1614G [to MR], Grant No. 01ZX1314K [to TGS]) and through NGFNplus MoodS (Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia) (Grant Nos. 01GS08144 and 01GS08147 [to MMN, MR, and SC]). This work was also supported by the Deutsche Forschungsgemeinschaft (Grant Nos. NO246/10-1 to MMN [FOR 2107], RI 908/11-1 to MR [FOR 2107], and WI 3429/3-1 [to SHW], and Grant Nos. SCHU 1603/4-1, SCHU 1603/5-1 [KFO 241], and SCHU 1603/7-1 [PsyCourse] [to TGS]), the Swiss National Science Foundation (Grant No. 156791 [to SC]), and the European Union (Grant No. N Health-F2-2008-222963 [to BTB and VA]). MMN is supported through the Excellence Cluster ImmunoSensation. TGS is supported by an unrestricted grant from the Dr. Lisa-Oehler Foundation. AJF received support from the BONFOR Programme of the University of Bonn, Germany. MH was supported by the Deutsche Forschungsgemeinschaft. BOMA-Romania: The work was supported by Unitatea Executiva Pentru Finantarea Invatamantului Superior a Cercetarii (Grant No. 89/2012 [to MG-S]). Bulgarian Trios: Recruitment was funded by the Janssen Research Foundation (Grant No. 045856), and genotyping was funded by multiple grants to the Stanley Center for Psychiatric Research at the Broad Institute from the Stanley Medical Research Institute, The Merck Genome Research Foundation, and the Herman Foundation (to GK). CoFaMS-Adelaide: Research was funded by the Australian NHMRC (Grant No. APP1060524 [to BTB]). CONVERGE: Research was funded by the Wellcome Trust (Grant Nos. WT090532/Z/09/Z, WT083573/Z/07/Z, and WT089269/Z/09/Z [to J Flint]) and the NIMH (Grant No. MH100549 [to KSK]). Danish RADIANT: Research was funded by Højteknologifonden (Grant No. 0001-2009-2 [to TW]) and the Lundbeck Foundation (Grant No. R24-A3242 [to TW]). deCODE: Research was funded by FP7-People-2011-IAPP grant agreement PsychDPC (Grant No. 286213 [to KS]) and the United States National Institute of Drug Abuse (Grant No. R01 DA017932 [to KS] and Grant No. R01 DA034076 [to TT]). Edinburgh: Genotyping was conducted at the Genetics Core Laboratory at the Clinical Research Facility (University of Edinburgh). Research was funded by the Wellcome Trust (Grant No. 104036/Z/14/Z [to AMM, T-KC, and DJP]). DJM is supported by a National Health Services Research Scotland Clinical Fellowship funded by the Chief Scientist Office. EGCUT: Research was funded by European Union Project (Grant Nos. EstRC-IUT20-60, 2014-2020.4.01.15-0012, and 692145 [to AM]). Fran: This research was supported by Fondation FondaMental, Créteil, France, and by the Investissements d'Avenir Programs managed by the Agence Nationale de la Recherche (Grant Nos. ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01 [to ML]). GenPOD/Newmeds: Research was funded by MRC (Grant No. G0200243 [to GL and MCO]), EU 6th Framework, (Grant No. LSHB-CT-2003-503428 [to RH]), IMI-JU (Grant No. 15008 [to GL]). GenScot: Research was funded by the UK Chief Scientist Office (Grant No. CZD/16/6 [to DJP]) and the Scottish Funding Council (Grant No. HR03006 [to DJP]). Genotyping was conducted at the Genetics Core Laboratory at the Clinical Research Facility (University of Edinburgh). GERA: Participants in the Genetic Epidemiology Research on Adult Health and Aging Study are part of

the Kaiser Permanente Research Program on Genes, Environment, and Health, supported by the National Institute on Aging, NIMH, Office of the Director (Grant No. RC2 AG036607 [to CS, N Risch]) and the Wayne and Gladys Valley Foundation, the Ellison Medical Foundation, the Robert Wood Johnson Foundation, and the Kaiser Permanente Regional and National Community Benefit Programs. GSK_Munich: Halifax: Halifax data were obtained with support from the Canadian Institutes of Health Research (Grant No. 64410 [to MA]). Harvard i2b2: Research was funded by NIMH (Grant No. R01 MH085542 [to JWS], Grant No. R01 MH086026 [to RHP]). iPSYCH: The iPSYCH (the Lundbeck Foundation Initiative for Integrative Psychiatric Research) team acknowledges funding from the Lundbeck Foundation (Grant Nos. R102-A9118 and R155-2014-1724, R129-A3973, and R24-A3243 [to TW, ADB, OM, MN, DH, and PBM]), the Stanley Medical Research Institute, the European Research Council (Grant No. 294838 [to TW, ADB, OM, MN, DH, and PBM]), the Novo Nordisk Foundation for supporting the Danish National Biobank resource, the Capital Region of Denmark (Grant No. R144-A5327 [to TW, ADB, OM, MN, DH, and PBM]), and grants from Aarhus and Copenhagen Universities and University Hospitals, including support to the iSEQ Center, the GenomeDK HPC facility, and the CIRRAU Center (to TW, ADB, OM, MN, DH, and PBM). Janssen: Funded by Janssen Research and Development, LLC. MARS/BDirect: This work was funded by the Max Planck Society, by the Max Planck Excellence Foundation, and by a grant from the BMBF in the National Genome Research Network framework (NGFN2 and NGFN-Plus) (Grant No. FKZ 01GS0481), and by the BMBF Program (Grant No. FKZ01ES0811). Controls were from the Dortmund Health Study that was supported by the German Migraine and Headache Society, and by unrestricted grants to the University of Münster from Almirall, AstraZeneca, Berlin Chemie, Boehringer, Boots Health Care, GlaxoSmithKline, Janssen Cilag, McNeil Pharma, MSD Sharp and Dohme, and Pfizer. Blood collection was funded by the Institute of Epidemiology and Social Medicine, University of Münster. Genotyping was supported by the BMBF (Grant Nos. 01ER0816 and 01ER1506 [to KB]). Mayo Bipolar Disorder Biobank: Research was funded by grants from the Marriot Foundation and the Mayo Clinic Center for Individualized Medicine (to JMB and MF). Michigan (NIMH/Pritzker Neuropsychiatric Disorders Research Consortium): Research was funded by NIMH (Grant Nos. R01 MH09414501A1 and MH105653 [to MB]). Many of the authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund, LLC. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, HudsonAlpha Institute of Biotechnology, the Universities of California at Davis, and at Irvine, to encourage the development of appropriate findings for research and clinical applications. Mount Sinai: This work was funded in part by a NARSAD Young Investigator award (to EAS), and by NIH (Grant Nos. R01MH106531 and R01MH109536 [to PS and EAS]). NeuRA-CASSI-Australia: This work was funded by the New South Wales Ministry of Health, Office of Health and Medical Research, and by the NHMRC (Grant No. 568807 [to CSW and TWW]). CSW was a recipient of NHMRC fellowships (Fellowship Nos. 1117079 and 1021970). NeuRA-IGP-Australia: Research was funded by the NHMRC (Grant Nos. 630471, 1061875, and 1081603 [to MJG]). NESDA: Research was funded by Nederlandse Organisatie voor Wetenschappelijk (ZonMW Geestkracht grant [to PWJHP]). Norway: Research was funded by the Vetenskapsrådet (to IA), the Western Norway Regional Health Authority (to KJO), the Research Council of Norway (Grant No. 421716 [to IM] and Grant Nos. 249711, 248778, 223273, and 217776 [to OAA]), the South-East Norway Regional Health Authority (Grant Nos. 2012-132 and 2012-131 [to OAA], Grant No. 2016-064 [to OBS], Grant No. 2017-004 [to OAA and OBS], Grant Nos. 2013-088, 2014-102, and 2011-085 [to IM]), and the KG Jebsen Stiftelsen (to OAA). TE was funded by the South-East Norway Regional Health Authority (Grant No. 2015-078) and a research grant from Mrs. Throne-Holst. NTR: Research was funded by Netherlands Organization for Scientific Research (Grant No. 480-15-001/674 [to DIB]). Pfizer: Research was funded by the EU Innovative Medicine Initiative Joint Undertaking (Grant No. 115008.5). PsyCoLaus: PsyCoLaus/CoLaus received additional support from research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (Grant Nos. 3200B0-105993, 3200B0-118308, 33CSO-122661, 33CSO-139468,

and 33CSO-148401 [to MP]). QIMR: Research was funded by NHMRC (Grant Nos. 941177, 971232, 3399450, and 443011 [to NGM]) and the National Institute on Alcohol Abuse and Alcoholism (Grant Nos. AA07535, AA07728, and AA10249 [to ACH]). RADIANT: Research was funded by MRC (Grant No. G0701420 [to GB and CML] and Grant No. G0901245 [to GB]) and NIMH (Grant No. U01 MH109528 [to GB]). Rotterdam Study: The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University and Netherlands Organization for Scientific Research (Grant Nos. 175.010.2005.011, 911-03-012 [to AGU]). SHIP-LEGEND/TREND: SHIP is part of the Community Medicine Research net of the University of Greifswald, which is funded by the Deutsche Forschungsgemeinschaft (Grant No. GR 1912/5-1 [to HJG]), Federal Ministry of Education and Research (Grant Nos. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs, and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Genotyping in SHIP was funded by Siemens Healthineers and the Federal State of Mecklenburg-West Pomerania. Genotyping in SHIP-TREND-0 was supported by the Federal Ministry of Education and Research (Grant No. 03ZIK012). Span2: Research was funded by Instituto de Salud Carlos III (Grant Nos. PI12/01139, PI14/01700, PI15/01789, and PI16/01505), and cofinanced by the European Regional Development Fund, Agència de Gestió d'Ajuts Universitaris i de Recerca-AGAUR, Generalitat de Catalunya (Grant No. 2014SGR1357), Departament de Salut, Generalitat de Catalunya, Spain, and a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation. This project has also received funding from the European Union's Horizon 2020 Research and Innovation Programme (Grant Nos. 667302 and 643051). CSM is a recipient of a Sara Borrell contract (Grant No. CD15/00199) and a mobility grant (Grant No. MV16/00039) from the Instituto de Salud Carlos III, Ministerio de Economía, Industria y Competitividad, Spain. MR is a recipient of a Miguel de Servet contract (Grant Nos. CP09/00119 and CPII15/00023) from the Instituto de Salud Carlos III, Ministerio de Economía, Industria y Competitividad, Spain. STAR*D: Research was funded by NIMH (Grant No. R01 MH-072802 [to SPH]). SUNY DMC: Research was funded by NIMH (Grant No. R01MH085542 [to CP, MTP, JAK, and HM]). SWEBIC: Research was funded by NIMH (Grant No. MH077139 [to ML]), the Vetenskapsrådet (Grant Nos. K2014-62X-14647-12-51 and K2010-61P-21568-01-4 [to ML]), the Swedish foundation for Strategic Research (Grant No. KF10-0039 [to ML]), and the Stanley Center for Psychiatric Research, Broad Institute from a grant from Stanley Medical Research Institute (to ML). Sweden: This work was funded by the Vetenskapsrådet (Grant No 2010-03631 [to MS and CL]), the Stockholm County Council (to MS, CL, LB, LF, and UÖ), and the Söderström Foundation (to LB). TwinGene: Research was funded by GenomeEUtwin, (Grant Nos. EU/QLRT-2001-01254 and QLG2-CT-2002-01254 [to NLP]), Heart and Lung Foundation (Grant No. 20070481 [to PKM]), Swedish Foundation for Strategic Research, and Vetenskapsrådet (Grant No. M-2005-1112 [to U de Faire]). UCL: Research was funded by the MRC (Grant No. G1000708 [to AM]). UCLA-Utrecht (Los Angeles): Research was funded by NIMH (Grant Nos. R01MH090553 and U01MH105578 [to NBF, RAO, LMOL, and APSO]). UK-BDRN: Research was funded by MRC Centre and Program Grants (Grant Nos. G0801418 and G0800509 [to MCO and MJO]), the Wellcome Trust (Grant No. 078901 [to NC, IJ, LAJ]), the Stanley Medical Research Institute (Grant No. 5710002223-01 [to NC, IJ, LAJ]), and a European Commission Marie Curie Fellowship (Grant No. 623932 [to ADF]). UK Biobank: This research has been funded by the NIHR under its BRCs funding initiative (Application Nos. 4844, 6818, and 16577 [to GB]) and the Wellcome Trust (Grant No. 04036/Z/14/Z [to AMM]). UNIBO/University of Barcelona, Hospital Clinic, IDIBAPS, CIBERSAM: This work was supported by the Spanish Ministry of Economy and Competitiveness (Grant No. PI15/00283 [to EV]) integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (Grant No. 2014 SGR 398). USC: Research funded by NIH (Grant No. R01MH085542 [to JLS]). WTCCC: The principal funder of this project was the Wellcome Trust (to NC and AHY). For the 1958 Birth Cohort, venous blood collection was funded by the UK MRC. AHY is funded by the NIHR BRC at South London and Maudsley NHS Foundation Trust and King's College London.

We are deeply indebted to the investigators who comprise the PGC, and to the hundreds of thousands of participants who have shared their life experiences with PGC investigators. BDRN acknowledges the research participants who continue to give their time to participate in our research. JMF thanks Janette M. O'Neil and Betty C. Lynch for their support. The deCODE authors are thankful to the participants and staff at the Patient Recruitment Center. GenPOD/Newmeds investigators are grateful to all the families who took part, the general practitioners and the Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants, and nurses. GlaxoSmithKline Munich investigators thank all participants in the GSK-Munich study. We also thank numerous people at GSK and Max Planck Institute, BKH Augsburg, and Klinikum Ingolstadt in Germany who contributed to this project. Janssen investigators are grateful to the study volunteers for participating in the research studies and to the clinicians and support staff for enabling patient recruitment and blood sample collection. We also thank the staff in the former Neuroscience Biomarkers of Janssen Research and Development for laboratory and operational support (e.g., biobanking, processing, plating, and sample de-identification), and to the staff at Illumina for genotyping Janssen DNA samples. MARS/BiDirect investigators acknowledge all study participants. We thank numerous people at Max Planck Institute, and all study sites in Germany and Switzerland who contributed to this project. Michigan investigators thank the participants who donated their time and DNA to make this study possible. We thank members of the NIMH Human Genetics Initiative and the University of Michigan Prechter Bipolar DNA Repository for generously providing phenotype data and DNA samples. QIMR investigators thank the twins and their families for their willing participation in our studies. STAR*D authors appreciate the efforts of the STAR*D investigator team for acquiring, compiling, and sharing the STAR*D clinical dataset. SWEBC investigators are deeply grateful for the participation of all participants contributing to this research, and to the collection team that worked to recruit them. We also wish to thank the Swedish National Quality Register for Bipolar Disorders: Bipolär. TwinGene investigators thank the Karolinska Institutet for infrastructural support of the Swedish Twin Registry. We thank the 23andMe research participants included in the analysis, all of whom provided informed consent and participated in the research online according to a human subjects protocol approved by an external AAHRPP-accredited institutional review board (Ethical & Independent Review Services), and the employees of 23andMe for making this work possible. 23andMe acknowledges the invaluable contributions of Michelle Agee, Babak Alipanahi, Adam Auton, Robert K. Bell, Katarzyna Bryc, Sarah L. Elson, Pierre Fontanillas, Nicholas A. Furlotte, David A. Hinds, Bethann S. Hromatka, Karen E. Huber, Aaron Kleinman, Nadia K. Litterman, Matthew H. McIntyre, Joanna L. Mountain, Carrie A.M. Northover, Steven J. Pitts, J. Fah Sathirapongsasuti, Olga V. Sazonova, Janie F. Shelton, Suyash Shringarpure, Chao Tian, Joyce Y. Tung, Vladimir Vacic, and Catherine H. Wilson.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

This article was published as a preprint on bioRxiv: doi: <https://doi.org/10.1101/383331>.

Genome-wide association study results from analyses including 23andMe are restricted by a data transfer agreement with 23andMe. For these analyses, linkage disequilibrium-independent sets of 10,000 single nucleotide polymorphisms have been made available via the Psychiatric Genetics Consortium (<https://www.med.unc.edu/pgc/results-and-downloads>). Summary statistics not including 23andMe have been made available via the Psychiatric Genetics Consortium (<https://www.med.unc.edu/pgc/results-and-downloads>).

O.A. Andreassen has received speaker fees from Lundbeck. A.T.F. Beekman is on speaker's bureau for Lundbeck and GlaxoSmithKline. G. Breen reports consultancy and speaker fees from Eli Lilly, Otsuka, and Illumina and grant funding from Eli Lilly. G. Crawford is a cofounder of Element Genomics. E. Domenici was formerly an employee of Hoffmann-La Roche and a consultant to Roche and Pierre Fabre. J. Nurnberger is an investigator for Janssen and was an investigator for Assurex. S.A. Paciga is an employee of Pfizer. J.A. Quiroz was formerly an employee of Hoffmann-

La Roche. S. Steinberg, H. Stefansson, K. Stefansson, and T.E. Thorgerisson are employed by deCODE Genetics/Amgen. P.F. Sullivan reports the following potentially competing financial interests: Current: Lundbeck (advisory committee, grant recipient). Past 3 years: Pfizer (scientific advisory board), Element Genomics (consultation fee), and Roche (speaker reimbursement). A.H. Young has given paid lectures and is on advisory boards for the following companies with drugs used in affective and related disorders: AstraZeneca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier, Liva-Nova. A.H. Young is lead investigator for Embolden Study (AstraZeneca), BCI Neuroplasticity study, and Aripiprazole Mania Study, which are investigator-initiated studies from AstraZeneca, Eli Lilly, Lundbeck, and Wyeth. All other authors declare no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Social, Genetic, and Developmental Psychiatry Centre (JRIC, HAG, GB), Institute of Psychiatry, Psychology, and Neuroscience, King's College London, and National Institute for Health Research Maudsley Biomedical Research Centre (JRIC, HAG, GB), King's College London, London, United Kingdom; and Department of Medical Epidemiology and Biostatistics (JB), Karolinska Institutet, Stockholm, Sweden.

The Bipolar Disorder and Major Depressive Disorder Working Groups of the Psychiatric Genomics Consortium are collaborative coauthors for this article. The individual authors are (numbers refer to affiliations listed in Supplement 1): Enda M. Byrne⁴, Andreas J. Forstner^{5,6,7,8,9}, Peter A. Holmans¹⁰, Christiaan A. de Leeuw¹¹, Manuel Mattheisen^{12,13,14,15,16}, Andrew McQuillin¹⁷, Jennifer M. Whitehead Pavlides¹⁸, Tune H. Pers^{19,20}, Stephan Ripke^{21,22,23}, Eli A. Stahl^{19,24,25}, Stacy Steinberg²⁶, Vassily Trubetskov²², Maciej Trzaskowski⁴, Yunpeng Wang^{27,28}, Liam Abbott²¹, Abdel Abdelou²⁹, Mark J. Adams³⁰, Annelie Nordin Adolfsson³¹, Esben Agerbo^{16,32,33}, Huda Akil³⁴, Diego Albani³⁵, Ney Alliey-Rodriguez³⁶, Thomas D. Als^{12,13,16}, Till F. M. Andlauer^{37,38}, Adebayo Anjorin³⁹, Verner Anttila²³, Sandra Van der Auwera⁴⁰, Swapnil Awasthi²², Silviu-Adrian Bacanu⁴¹, Judith A. Badner⁴², Marie Bækvad-Hansen^{16,43}, Jack D. Barchas⁴⁴, Nicholas Bass¹⁷, Michael Bauer⁴⁵, Aartjan T. F. Beekman⁴⁶, Richard Belliveau²¹, Sarah E. Bergen³, Tim B. Bigdeli^{41,47}, Elisabeth B. Binder^{37,48}, Erlend Bøen⁴⁹, Marco Boks⁵⁰, James Boocock⁵¹, Monika Budde⁵², William Bunney⁵³, Margit Burmeister⁵⁴, Henriette N. Buttenschøn^{3,12,55}, Jonas Bybjerg-Grauholm^{16,43}, William Byerley⁵⁶, Na Cai^{57,58}, Miquel Casas^{59,60,61,62}, Enrique Castelao⁶³, Felecia Cerrato²¹, Pablo Cervantes⁶⁴, Kimberly Chambert²¹, Alexander W. Charney²⁵, Danfeng Chen²¹, Jane Hvarregaard Christensen^{12,13,55}, Claire Churchhouse^{21,23}, David St Clair⁶⁵, Toni-Kim Clarke³⁰, Lucia Colodro-Conde⁶⁶, William Coryell⁶⁷, Baptiste Couvy-Duchesne^{18,68}, David W. Craig⁶⁹, Gregory E. Crawford^{70,71}, Cristiana Cruceanu^{37,64}, Piotr M. Czerski⁷², Anders M. Dale^{73,74,75,76}, Gail Davies⁷⁷, Ian J. Deary⁷⁷, Franziska Degenhardt^{7,8}, Jurgen Del-Favero⁷⁸, J. Raymond DePaulo⁷⁹, Eske M. Derks⁸⁶, Nese Direk^{80,81}, Srđan Djurovic^{82,83}, Amanda L. Dobbyn^{24,25}, Conor V. Dolan²⁹, Ashley Dumont²¹, Erin C. Dunn^{21,84,85}, Thalia C. Eley¹, Torbjørn Elvsåshagen^{86,87}, Valentina Escott-Price¹⁰, Chun Chieh Fan⁷⁶, Hilary K. Finucane^{88,89}, Sascha B. Fischer^{5,9}, Matthew Flickinger⁹⁰, Jerome C. Foer⁹¹, Tatiana M. Foroud⁹², Liz Forty¹⁰, Josef Frank⁹¹, Christine Fraser¹⁰, Nelson B. Freimer⁹³, Louise Frisén^{94,95,96}, Katrin Gade^{52,97}, Diane Gage²¹, Julie Garnham⁹⁸, Claudia Giambartolomei⁵¹, Fernando S. Goes⁹⁹, Jacqueline Goldstein²¹, Scott D. Gordon⁶⁶, Katherine Gordon-Smith¹⁰⁰, Elaine K. Green¹⁰¹, Melissa J. Green¹⁰², Tiffany A. Greenwood⁷⁵, Jakob Grove^{12,13,16,103}, Weihua Guan¹⁰⁴, Lynsey S. Hall^{30,105}, Marian L. Hamshere¹, Christine Søholm Hansen^{16,43}, Thomas F. Hansen^{16,106,107}, Martin Hautzinger¹⁰⁸, Urs Heilbronner⁵², Albert M. van Hemert¹⁰⁹, Stefan Herms^{5,7,8,9}, Ian B. Hickie¹¹⁰, Maria Hipolito¹¹¹, Per Hoffmann^{5,7,8,9}, Dominic Holland^{73,112}, Georg Homuth¹¹³, Carsten Horn¹¹⁴, Jouke-Jan Hottenga²⁹, Laura Huckins^{24,25}, Marcus Ising¹⁵, Stéphane Jamain^{116,117}, Rick Jansen⁴⁶, Jessica S. Johnson^{24,25}, Simone de Jong^{1,2}, Eric Jorgensen¹¹⁸, Anders Jureus³, Radhika Kandaswamy¹, Robert Karlsson³, James L. Kennedy^{119,120,121,122}, Farnush Farhadi Hassan Kiadeh¹²³, Sarah Kittel-Schneider¹²⁴, James A. Knowles^{125,126}, Manolis Kogevinas¹²⁷, Isaac S. Kohane^{128,129,130}, Anna C. Koller^{7,8}, Julia Kraft²², Warren W. Kretschmar¹³¹, Jesper Krogh¹³², Ralph Kupka^{46,133}, Zoltán Kutalik^{134,135}, Catharina Lavebratt⁹⁴, Jacob Lawrence¹³⁶, William B. Lawson¹¹¹, Markus Leber¹³⁷,

- Phil H. Lee^{21,23,138}, Shawn E. Levy¹³⁹, Jun Z. Li¹⁴⁰, Yihan Li¹³¹, Penelope A. Lind⁶⁶, Chunyu Liu¹⁴¹, Loes M. Olde Loohuis⁹³, Anna Maaser^{7,8}, Donald J. MacIntyre^{142,143}, Dean F. MacKinnon⁹⁹, Pamela B. Mahon^{79,144}, Wolfgang Maier¹⁴⁵, Robert M. Maier¹⁸, Jonathan Marchini¹⁴⁶, Lina Martinsson⁹⁵, Hamdi Mbarek²⁹, Steve McCarroll^{21,147}, Patrick McGrath¹⁴⁸, Peter McGuffin¹, Melvin G. McInnis¹⁴⁹, James D. McKay¹⁵⁰, Helena Medeiros¹²⁶, Sarah E. Medland⁶⁶, Divya Mehta^{18,151}, Fan Meng^{34,149}, Christel M. Middeldorp^{29,152,153}, Evelin Mihailov¹⁵⁴, Yuri Milaneschi¹⁴⁶, Lili Milani¹⁵⁴, Saira Saeed Mirza⁹⁰, Francis M. Mondimore⁹⁹, Grant W. Montgomery⁴, Derek W. Morris^{155,156}, Sara Mostafavi^{157,158}, Thomas W. Mühleisen^{5,159}, Niamh Mullins¹, Matthias Nauck^{160,161}, Bernard Ng¹⁵⁸, Hoang Nguyen^{24,25}, Caroline M. Nievergelt^{75,162}, Michel G. Nivard²⁹, Evaristus A. Nwulia¹¹¹, Dale R. Nyholt¹⁶³, Claire O'Donovan⁹⁸, Paul F. O'Reilly¹, Anil P. S. Ori⁹³, Lilijana Oruc¹⁶⁴, Urban Ösby¹⁶⁵, Hogni Oskarsson¹⁶⁶, Jodie N. Painter⁶⁶, José Guzman Parra¹⁶⁷, Carsten Bøcker Pedersen^{16,32,33}, Marianne Giørtz Pedersen^{16,32,33}, Amy Perry¹⁰⁰, Roseann E. Peterson^{41,168}, Erik Pettersson³, Wouter J. Peyrot¹⁴⁶, Andrea Pennig⁴⁵, Giorgio Pistis⁶³, Shaun M. Purcell^{25,144}, Jorge A. Quiroz¹⁶⁹, Per Qvist^{2,13,55}, Eline J. Regeer¹⁷⁰, Andreas Reif¹²⁴, Céline S. Reinbold^{5,9}, John P. Rice¹⁷¹, Brien P. Riley⁴¹, Fabio Rivas¹⁶⁷, Margarita Rivera^{1,172}, Panos Roussos^{24,25,173}, Douglas M. Ruderfer¹⁷⁴, Euijung Ryu¹⁷⁵, Cristina Sánchez-Mora^{59,60,62}, Alan F. Schatzberg¹⁷⁶, William A. Scheftner¹⁷⁷, Robert Schoevers¹⁷⁸, Nicholas J. Schork¹⁷⁹, Eva C. Schulte^{52,180}, Tatyana Shekhtman⁷⁵, Ling Shen¹¹⁸, Jianxin Shi¹⁸¹, Paul D. Shilling⁷⁵, Stanley I. Shyn¹⁸², Engilbert Sigurdsson¹⁸³, Claire Slaney⁹⁸, Olav B. Smeland^{73,184,185}, Johannes H. Smit⁴⁶, Daniel J. Smith¹⁸⁶, Janet L. Sobel¹⁸⁷, Anne T. Spijker¹⁸⁸, Michael Steffens¹⁸⁹, John S. Strauss^{121,190}, Fabian Streit⁹¹, Jana Strohmaier⁹¹, Szabolcs Szelinger¹⁹¹, Katherine E. Tansey¹⁹², Henning Teismann¹⁹³, Alexander Teumer¹⁹⁴, Robert C. Thompson¹⁴⁹, Wesley Thompson^{55,75,87,107}, Pippa A. Thomson¹⁹⁵, Thorgerir E. Thorgerirsson²⁶, Matthew Traylor¹⁹⁶, Jens Treutlein⁹¹, André G. Uitterlinden¹⁹⁷, Daniel Umbricht¹⁹⁸, Helmut Vedder¹⁹⁹, Alexander Viktorin³, Peter M. Visscher^{4,18}, Weiqing Wang^{24,25}, Stanley J. Watson¹⁴⁹, Bradley T. Webb¹⁶⁸, Cynthia Shannon Weickert^{102,200}, Thomas W. Weickert^{102,200}, Shantel Marie Weinsheimer^{55,107}, Jürgen Wellmann¹⁹³, Gonneke Willemsen²⁹, Stephanie H. Witt⁹¹, Yang Wu⁴, Hualin S. Xi²⁰¹, Wei Xu^{202,203}, Jian Yang^{4,18}, Allan H. Young²⁰⁴, Peter Zandi²⁰⁵, Peng Zhang²⁰⁶, Futao Zhang⁴, Sebastian Zollner¹⁴⁹, Rolf Adolfsson³¹, Ingrid Agartz^{14,49,207}, Martin Alda^{98,208}, Volker Arolt²⁰⁹, Lena Backlund⁹⁵, Bernhard T. Baune²¹⁰, Frank Bellivier^{211,212,213,214}, Klaus Berger¹⁹³, Wade H. Berrettini²¹⁵, Joanna M. Bieracka¹⁷⁵, Douglas H. R. Blackwood³⁰, Michael Boehnke⁹⁰, Dorret I. Boomsma²⁹, Aiden Corvin¹⁵⁶, Nicholas Craddock¹⁰, Mark J. Daly^{21,23}, Udo Dannlowski²⁰⁹, Enrico Domenici²¹⁶, Katharina Domschke²¹⁷, Tõnu Esko^{19,147,154,218}, Bruno Etain^{211,213,214,219}, Mark Frye²²⁰, Janice M. Fullerton^{200,221}, Elliot S. Gershon^{36,222}, EJC de Geus^{29,223}, Michael Gill¹⁵⁶, Fernando Goes⁷⁹, Hans J. Grabe⁴⁰, Maria Grigoriou-Serbanescu²²⁴, Steven P. Hamilton²²⁵, Joanna Hauser⁷², Caroline Hayward²²⁶, Andrew C. Heath¹⁷¹, David M. Hougaard^{16,43}, Christina M. Hultman³, Ian Jones¹⁰, Lisa A. Jones¹⁰⁰, René S. Kahn^{25,50}, Kenneth S. Kendler⁴¹, George Kirov¹⁰, Stefan Kloiber^{115,121,190}, Mikael Landén^{3,227}, Marion Leboyer^{117,211,228}, Glyn Lewis¹⁷, Qingqin S. Li²²⁹, Jolanta Lissowska²³⁰, Susanne Lucae¹¹⁵, Pamela A. F. Madden¹¹⁹, Patrik K. Magnusson³, Nicholas G. Martin^{66,231}, Fermin Mayoral¹⁶⁷, Susan L. McElroy²³², Andrew M. McIntosh^{30,77}, Francis J. McMahon²³³, Ingrid Melle^{234,235}, Andres Metspalu^{154,236}, Philip B. Mitchell¹⁰², Gunnar Morken^{237,238}, Ole Mors^{16,239}, Preben Bo Mortensen^{12,16,32,33}, Bertram Müller-Myhsok^{37,240,241}, Richard M. Myers¹³⁹, Benjamin M. Neale^{19,21,23}, Vishwajit Nimgaonkar²⁴², Merete Nordentoft^{16,243}, Markus M. Nöthen^{7,8}, Michael C. O'Donovan¹⁰, Ketil J. Oedegaard^{244,245}, Michael J. Owen¹⁰, Sara A. Paciga²⁴⁶, Carlos Pato^{126,247}, Michele T. Pato¹²⁶, Nancy L. Pedersen³, Brenda W. J. H. Penninx⁴⁶, Roy H. Perlis^{248,249}, David J. Porteous¹⁹⁵, Danielle Posthuma^{11,250}, James B. Potash⁷⁹, Martin Preisig⁶³, Josep Antoni Ramos-Quiroga^{59,60,61,62}, Marta Ribasés^{59,60,62}, Marcella Rietschel⁹¹, Guy A. Rouleau^{251,252}, Catherine Schaefer¹¹⁸, Martin Schalling⁹⁴, Peter R. Schofield^{200,221}, Thomas G. Schulze^{52,79,91,97,233}, Alessandro Serretti²⁵³, Jordan W. Smoller^{21,84,85}, Hreinn Stefansson²⁶, Kari Stefansson^{26,254}, Eysteinn Stordal^{255,256}, Henning Tiemeier^{80,257,258}, Gustavo Turecki²⁵⁹, Rudolf Uher⁹⁸, Arne E. Vaaler²⁶⁰, Eduard Vieta²⁶¹, John B. Vincent¹⁹⁰, Henry Völzke¹⁹⁴, Myrna M. Weissman^{148,262}, Thomas Werge^{16,107,263}, Ole A. Andreassen^{184,185}, Anders D. Børglum^{12,13,16}, Sven Cichon^{5,7,9,159}, Howard J. Edenberg²⁶⁴, Arianna Di Florio^{10,265}, John
- Kelsoe⁷⁵, Douglas F. Levinson¹⁷⁶, Cathryn M. Lewis^{1,2,266}, John I. Nurnberger^{92,267}, Roel A. Ophoff^{50,51,93}, Laura J. Scott⁹⁰, Pamela Sklar^{24,251}, Patrick F. Sullivan^{3,265,268}, and Naomi R. Wray^{4,18}.
- Address correspondence to Jerome Breen, Ph.D., Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, London, SE5 8AF, United Kingdom; E-mail: gerome.breen@kcl.ac.uk.
- Received May 2, 2019; revised Sep 27, 2019; accepted Oct 15, 2019.
Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.biopsych.2019.10.015>.

REFERENCES

- Craddock N, Owen MJ (2010): The Kraepelinian dichotomy—going, going . . . but still not gone. *Br J Psychiatry* 196:92–95.
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62:593–602.
- Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, *et al.* (1996): Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 276:293–299.
- Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D (2014): The global prevalence of common mental disorders: A systematic review and meta-analysis 1980–2013. *Int J Epidemiol* 43:476–493.
- American Psychiatric Association (1980): *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington, DC: American Psychiatric Press.
- Reed GM, First MB, Kogan CS, Hyman SE, Gureje O, Gaebel W, *et al.* (2019): Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry* 18:3–19.
- American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA: American Psychiatric Association Publishing.
- Cassano GB, Rucci P, Frank E, Fagioli A, Dell'Oso L, Shear MK, Kupfer DJ (2004): The mood spectrum in unipolar and bipolar disorder: Arguments for a unitary approach. *Am J Psychiatry* 161:1264–1269.
- Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH (2011): Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am J Psychiatry* 168:40–48.
- Ratheesh A, Davey C, Hetrick S, Alvarez-Jimenez M, Voutier C, Bechdolf A, *et al.* (2017): A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. *Acta Psychiatr Scand* 135:273–284.
- National Collaborating Centre for Mental Health (United Kingdom) (2012): *Common Mental Health Disorders: Identification and Pathways to Care*. Leicester, United Kingdom: British Psychological Society.
- National Collaborating Centre for Mental Health (United Kingdom) (2018): *Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care*. Leicester, United Kingdom: British Psychological Society.
- Polderman TJC, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, Posthuma D (2015): Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* 47:702–709.
- McGuffin P, Rijdsdijk F, Andrew M, Sham P, Katz R, Cardno A (2003): The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 60:497–502.
- Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50:668–681.
- Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, *et al.* (2019): Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet* 55:793–803.

17. The Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, *et al.* (2018): Analysis of shared heritability in common disorders of the brain. *Science* 360:eaap8757.
18. Davis KAS, Coleman JRI, Adams M, Allen N, Breen G, Cullen B, *et al.* (2019): Mental health in UK Biobank. Revised. medrxiv 19001214; doi: <https://doi.org/10.1101/19001214>.
19. Coleman JRI, Peyrot WJ, Purves KL, Davis KAS, Rayner C, Choi SW, *et al.* (2019): Genome-wide gene-environment analyses of depression and reported lifetime traumatic experiences in UK Biobank. bioRxiv 247353; doi: <https://doi.org/10.1101/247353>.
20. Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, *et al.* (2016): Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nat Genet* 48:1031–1036.
21. Gilly A, Tachmazidou I, Zeggini E (2015): Meta-analysis of summary statistics from quantitative trait association studies with unknown sample overlap. *Genet Epidemiol* 39:552–553.
22. Southam L, Gilly A, Süveges D, Farmaki A-E, Schwartzentruber J, Tachmazidou I, *et al.* (2017): Whole genome sequencing and imputation in isolated populations identify genetic associations with medically-relevant complex traits. *Nat Commun* 8:15606.
23. Turley P, Walters RK, Maghazian O, Okbay A, Lee JJ, Fontana MA, *et al.* (2018): Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat Genet* 50:229–237.
24. Hill WD (2018): Comment on “Large-Scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets” by Lam *et al.* *Twin Res Hum Genet* 21:84–88.
25. Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, *et al.* (2015): LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 47:291–295.
26. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, *et al.* (2019): International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat Commun* 10:4558.
27. Shi H, Kichaev G, Pasaniuc B (2016): Contrasting the genetic architecture of 30 complex traits from summary association data. *Am J Hum Genet* 99:139–153.
28. Shi H, Mancuso N, Spendlove S, Pasaniuc B (2017): Local genetic correlation gives insights into the shared genetic architecture of complex traits. *Am J Hum Genet* 101:737–751.
29. R Core Team (2015): R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: <http://www.r-project.org>. Accessed September 6, 2019.
30. Warnes GR, Bolker B, Bonebakker L, Gentleman R, Liaw WH, Lumley T, *et al.* (2016): Gplots: Various R programming tools for plotting data, version 3.0.1. Available at: <https://CRAN.R-project.org/package=gplots>. Accessed September 6, 2019.
31. Purves KL, Coleman JRI, Meier SM, Rayner C, Davis KAS, Cheesman R, *et al.* (2019): A major role for common genetic variation in anxiety disorders [published online ahead of print Nov 20]. *Mol Psychiatry*.
32. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511:421–427.
33. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 51:63–75.
34. Baselmans BML, Bartels M (2018): A genetic perspective on the relationship between eudaimonic and hedonic well-being. *Sci Rep* 8:14610.
35. Baselmans BML, Jansen R, Ip HF, van Dongen J, Abdellaoui A, van de Weijer MP, *et al.* (2019): Multivariate genome-wide analyses of the well-being spectrum. *Nat Genet* 51:445–451.
36. Choi SW, O'Reilly PF (2019): PRSice-2: Polygenic risk score software for biobank-scale data. *Gigascience* 8:giz082.
37. de Leeuw CA, Mooij JM, Heskes T, Posthuma D (2015): MAGMA: Generalized gene-set analysis of GWAS data. *PLoS Comput Biol* 11:e1004219.
38. Skene NG, Bryois J, Bakken TE, Breen G, Crowley JJ, Gaspar HA, *et al.* (2018): Genetic identification of brain cell types underlying schizophrenia. *Nat Genet* 50:825–833.
39. GTEx Consortium, Laboratory, Data Analysis & Coordinating Center (LDACC)—Analysis Working Group, Statistical Methods groups—Analysis Working Group, Enhancing GTEx (eGTEx) groups, NIH Common Fund, NIH/NCI, *et al.* (2017): Genetic effects on gene expression across human tissues. *Nature* 550:204–213.
40. Finucane HK, Reshef YA, Anttila V, Slowikowski K, Gusev A, Byrnes A, *et al.* (2018): Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat Genet* 50:621–629.
41. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R, *et al.* (2018): Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat Commun* 9:224.
42. Yang J, Lee SH, Goddard ME, Visscher PM (2011): GCTA: A tool for genome-wide complex trait analysis. *Am J Hum Genet* 88:76–82.
43. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, *et al.* (2018): Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 50:912–919.
44. Lee JJ, Wedow R, Okbay A, Kong E, Maghazian O, Zacher M, *et al.* (2018): Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet* 50:1112–1121.
45. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, *et al.* (2015): Genetic studies of body mass index yield new insights for obesity biology. *Nature* 518:197–206.
46. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, *et al.* (2017): Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet* 49:1385–1391.
47. Loh P-R, Kichaev G, Gazal S, Schoech AP, Price AL (2018): Mixed-model association for biobank-scale datasets. *Nat Genet* 50:906–908.
48. Howard DM, Adams MJ, Shirali M, Clarke T-K, Marioni RE, Davies G, *et al.* (2018): Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nat Commun* 9:1470.
49. Li X, Luo Z, Gu C, Hall LS, McIntosh AM, Zeng Y, *et al.* (2018): Common variants on 6q16.2, 12q24.31 and 16p13.3 are associated with major depressive disorder. *Neuropsychopharmacology* 43:2146–2153.
50. Okbay A, Baselmans BML, De Neve J-E, Turley P, Nivard MG, Fontana MA, *et al.* (2016): Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet* 48:624–633.
51. Amare AT, Vaez A, Hsu YH, Direk N, Kamali Z, Howard DM, *et al.* (2019): Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or schizophrenia reveal eight novel genetic loci for depression [published online ahead of print Jan 9]. *Mol Psychiatry*.
52. Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, *et al.* (2019): Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci* 22:343–352.
53. Jiang Y, Zhang H (2011): Propensity score-based nonparametric test revealing genetic variants underlying bipolar disorder. *Genet Epidemiol* 35:125–132.
54. Ikeda M, Takahashi A, Kamatani Y, Okahisa Y, Kunugi H, Mori N, *et al.* (2018): A genome-wide association study identifies 2 novel susceptibility loci and trans population polygenicity associated with bipolar disorder. *Mol Psychiatry* 23:639–647.
55. Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011): Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 43:977–983.
56. Charney AW, Ruderfer DM, Stahl EA, Moran JL, Chambert K, Belliveau RA, *et al.* (2017): Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Transl Psychiatry* 7:e993.

57. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, *et al.* (2018): Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat Genet* 50:920–927.
58. Smith DJ, Escott-Price V, Davies G, Bailey MES, Colodro-Conde L, Ward J, *et al.* (2016): Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol Psychiatry* 21:749–757.
59. Luciano M, Hagenaars SP, Davies G, Hill WD, Clarke T-K, Shirali M, *et al.* (2018): Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism. *Nat Genet* 50:6–11.
60. Li Z, Chen J, Yu H, He L, Xu Y, Zhang D, *et al.* (2017): Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. *Nat Genet* 49:1576–1583.
61. Cross-Disorder Group of the Psychiatric Genomics Consortium (2013): Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet* 381:1371.
62. National Institute for Healthcare and Excellence (2009): Depression in Adults: Recognition and Management: Clinical Guideline [CG90]. Available at <https://www.nice.org.uk/guidance/cg90>. Accessed September 6, 2019.
63. Coleman JRI, Bryois J, Gaspar HA, Jansen PR, Savage JE, Skene N, *et al.* (2019): Biological annotation of genetic loci associated with intelligence in a meta-analysis of 87,740 individuals. *Mol Psychiatry* 24:182–197.
64. Verbanck M, Chen C-Y, Neale B, Do R (2018): Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 50:693–698.
65. Hemani G, Bowden J, Davey Smith G (2018): Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet* 27:R195–R208.
66. Carney RM, Freedland KE (2017): Depression and coronary heart disease. *Nat Rev Cardiol* 14:145–155.
67. Weissbrod O, Flint J, Rosset S (2018): Estimating SNP-based heritability and genetic correlation in case-control studies directly and with summary statistics. *Am J Hum Genet* 103:89–99.
68. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, *et al.* (2018): Psychiatric genomics: An update and an agenda. *Am J Psychiatry* 175:15–27.